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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/686,809	10/17/2003	Bernd Nickel	017094-0306034	8786

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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 10/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/686,809	NICKEL ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-29* is/are rejected.

7)☒ Claim(s) *20, 23, 25 and 26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1 sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 14-29 are currently pending. This is the first Office Action on the merits of the application.

Election/Restrictions

Applicant's election of the specie N-(pyridine-4-yl)-[1-(4-cholorbenzyl)-indole-3-yl]glyoxamide (D 24851; Indibulin) in the reply filed on 9/18/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election **without traverse** (MPEP § 818.03(a)).

Priority

Acknowledgment is made of applicant's claim for foreign priority based on applications filed in Germany on 9/28/1999 and 4/2/1998. It is noted, however, that applicant has not filed a certified copy of the DE 19946301.8 and DE 19814838.0 applications as required by 35 U.S.C. § 119(b).

Applicant is reminded that in order for a patent issuing on the instant application to obtain the benefit of priority based on priority papers filed in parent Application No. 09/492,531 under 35 U.S.C. § 119(a)-(d) or (f), a claim for such foreign priority must be timely made in this application. To satisfy the requirement of 37 CFR § 1.55(a)(2) for a certified copy of the foreign application, applicant may simply identify the application containing the certified copy.

Information Disclosure Statement

The Information Disclosure Statement filed 10/13/2003 has been received and the references therein considered by the examiner to the extent each is a proper citation.

Specification

The disclosure is objected to because of the following informalities: the specification is replete with misspelled words and grammatical errors. Recognized misspellings and grammatical errors occur on page 1, line 35; page 3, lines 14 and 21; page 5, lines 4 and 7; page 9, line 3; and page 12, lines 9, 14, 20 and 24. Further, page 12, line 25 refers to a compound of "general formula 1a". However, there is no compound of general formula "1a" in the claims.

Claim Objections

Claim 20 is objected to because of the following informalities: the word "or" between "salt" and "an organic acid" should be ---of---. Appropriate correction is required.

Claims 23, 25 and 26 are objected to because of the following informalities: the words "doxirubicine" and "epotholone B" are misspelled. The correct spellings are ---doxorubicin--- and ---epothilone B---. Appropriate correction is required.

Claim Rejections - 35 USC § 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-29 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is a lack of enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) The breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to the treatment of resistant tumors, metastasizing tumors or tumors sensitive to angiogenesis inhibitors. The relative skill of those in the art is high, generally that of an M.D. or Ph.D. That factor is outweighed, however, by the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites Gura, T. (Science, 1997, 278:1041-1042) and Johnson *et al.* (British J. of Cancer, 2001, 84(10):1424-1431).

Gura, cited for evidentiary purposes, teaches that researchers face the problem of sifting through potential anticancer agents to find the ones promising enough to make human clinical

trials worthwhile and further teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second paragraphs). It is noted that he pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. Also, with regard to unpredictability, Johnson *et al.*, also cited for evidentiary purposes, teach that the *in vivo* activity of 39 different agents in a particular histology in a tumor model did not correlate to activity in the same human cancer. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Further, the mode of action of anticancer agents is often unknown or very unpredictable and administration of such agents is often accompanied by undesirable side effects.

These articles plainly demonstrate that the art of treating cancer, particularly in humans, is extremely unpredictable, particularly in the case of a single compound or genus of compounds being used to treat any and all cancers.

2. The breadth of the claims

The claims vary in breadth; some (such as claim 1) vary broadly, reciting the treatment of tumors with a broad genus of compounds. Others, such as claims 19 and 29, are narrower, reciting specific species of the claimed genus of compounds. All, however, are extremely broad insofar as they disclose the general treatment of resistant and metastasizing tumors with the same compounds.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the particular administration regimes (dosages, timing, administration routes, etc.) necessary to treat all of the various tumors claimed, particularly in humans. The working examples are limited to: 1) the *in vitro* cytotoxic effects of one compound, D-24851, on one multidrug resistant leukemia cell line; 2) the inhibition of metastasis of MO4 fibrosarcoma cells by D-24851; and 3) the antiangiogenic effect of D-24851.[2] Thus, the applicant at best has provided specific direction or guidance only for the treatment of a single multidrug resistant leukemia cell line and a single metastasizing cell line with a specific compound (D-24851). No reasonably specific guidance is provided concerning useful therapeutic protocols for any other tumors.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed compound (D-24851) could be predictably used as a treatment for all resistant tumors, metastasizing tumors and tumors sensitive to angiogenesis inhibitors as inferred in the claims and contemplated by the specification. In the case of "resistant tumors" the specification only describes one multidrug resistant leukemia cell line (page 9, lines 11-32). No methods for testing whether or not any particular tumor is "resistant" are provided. Dependent claim 23 limits the resistant tumors to those that are resistant to taxol,

[2] Examiner notes that leukemia is a blood-borne cancer, not a "tumor" *per se*.

doxorubicine, vincristine or epothilone B. Similarly, in the case of "metastasizing tumors", only one such example is provided (MO4 fibrosarcoma cells) (page 9, line 34 to page 10, line 20). Finally, in the case of "tumors sensitive to angiogenesis inhibitors", applicants have provided neither examples of such tumors nor any methods for one skilled in the art to identify a tumor sensitive to an angiogenesis inhibitor. Applicants only describe the effects of one compound on inhibition of endothelial cell vascularization; no specific tumors sensitive to angiogenesis inhibitors or methods of identifying such tumors are described. Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claims 14-29 are rejected under 35 U.S.C. § 112, first paragraph, as based on a disclosure which is not enabling. The synthesis of the claimed compounds, critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

In the instant case, the claimed compounds are required to be administered to a patient. However, the specification does not set forth any procedures or synthetic methodology to synthesize the claimed compounds. Applicants state that the claimed compounds are described in German Application 19814 838.0 (page 3, lines 14-15). However, this is insufficient to enable one skilled in the art to make and isolate the claimed compounds.

The incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper. Applicant is

required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR § 1.57(f).

Claims 14-29 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

In the instant case, claims 14, 19 and 29 recite compounds and "N-oxides" thereof. Claims dependent from claims 14, 19 and 29 carry forth this limitation and are included in this rejection. There is insufficient written description for said N-oxides in the specification.

M.P.E.P. § 2163 states, "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention...one must define a compound by 'whatever characteristics sufficiently distinguish it'. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process."

An N-oxide is, in the strictest sense, an oxide of a tertiary amine but is often used to describe oxides of primary and secondary amines. The compounds recited in the instant claims contain multiple amine functionalities (primary, secondary and tertiary). As such, without specific guidance and description in the specification, one skilled in the art is not apprised of the detailed chemical structures of compounds containing an N-oxide. The specification only states that the N-oxides of the recited compounds are within the scope of the invention (*e.g.* page 4, line 20) but does not provide any examples of such compounds, either in structure or named compounds. As such, it is not clear that applicants had possession of the claimed subject matter at the time the invention was made.

Claim Rejections - 35 USC § 112 – Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-29 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 recites the administration of "an effective amount" of a compound of formula (I). This limitation is indefinite because it is not clear what the amount being administered is effective for. The preamble of the claim is not linked to the body of the claim in such a way as to clearly convey that the "effective amount" being administered is effective to treat the condition recited in the preamble. The phrase "an effective amount" has been held to be

indefinite when the claim fails to state the function which is to be achieved and more than one effect can be implied from the specification or the relevant art. *In re Fredericksen* 213 F.2d 547, 102 USPQ 35 (CCPA 1954). Claims dependent from claim 14 are included in this rejection as they carry forth this limitation.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 14-29 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 6,232,327. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant claims and the claims of the '327 patent are drawn to the treatment of tumors with the same compounds. One skilled in the art would recognize that "resistant tumors", "metastasizing tumors" and "tumors sensitive to angiogenesis inhibitors" are all within the scope of the '327 patent. Further, the "comprising" language of the '327 patent allows for the administration of other compounds, including the instantly claimed antitumor agents.

Claims 14-29 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2-6, 10 and 12 of U.S. Patent No. 6,693,119. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant claims and the claims of the '119 patent are drawn to the treatment of tumors with the same compounds. Further, the "comprising" language of the '119 patent allows for the administration of other compounds, including the instantly claimed antitumor agents.

Claims 14, 18, 19 and 23-29 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 11-14 and 16-23 of copending Application No. 10/309,204. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims read on the claims of the '204 application when the compounds are used to treat the cancers recited in '204. For example, one skilled in the art would recognize that prostate carcinoma (recited in the claims of '204) is a

"metastasizing tumor" as instantly claimed. Further, the "comprising" language of the '204 application allows for the administration of other compounds, including the instantly claimed antitumor agents.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Patent Examiner
AU 1614

September 22, 2006

Ardin H. Marschel 9/29/06
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SUPERVISORY PATENT EXAMINER